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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

RAWLINGS, STEPHEN L

ART UNIT	PAPER NUMBER
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1643

DATE MAILED: 01/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

SUPPLEMENTAL
Office Action Summary

Application No.

09/581,651

Applicant(s)

SCHOR ET AL

Examiner

Stephen L. Rawlings, Ph.D.

Art Unit

1643

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 6/8/05, 8/18/05, and 11/10/05.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,4,5,7-9,29,60 and 61 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 29 is/are allowed.
- 6) ☒ Claim(s) 1,4,5,7-9,60 and 61 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 6/8/05 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

NOTE: The following is a supplement to the immediate prior Office action, which may not clearly indicate the withdrawal of the previous indication of allowability of claims 4 and 5. As again noted below in section 8, the indicated allowability of claims 4 and 5 is withdrawn in view of the new grounds of rejection of those claims set forth herein. The Examiner regrets any confusion or inconvenience resulting from any lack of clarity in the prior Office action, as to present status of claims 4 and 5.

This Office action is otherwise unchanged, relative to the immediate prior Office action.

1. The amendment filed November 10, 2005, is acknowledged and has been entered. Claims 2, 3, 10, 11, 26-42, 44, 47-51, 53, 56, and 58 have been canceled. Claims 1, 4, 5, 8, 9, and 29 have been amended. Claims 60 and 61 have been added.

2. The amendment filed August 18, 2005, is acknowledged and has been entered. Claims 6, 12, 13, 27, 57, and 59 have been canceled. Claims 1, 2, 4, 5, 8-11, 29, 36-38, 40-42, 47, 51, 56, and 58 have been amended.

3. The amendment filed June 8, 2005, is acknowledged and has been entered in part.

4. Claims 1, 4, 5, 7-9, 29, 60, and 61 are currently under prosecution.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

6. The requirement to elect a species of the invention of Group I set forth in section 8 of the Office action mailed May 3, 2002, has been withdrawn.

Drawings

7. Receipt of the replacement drawings filed June 8, 2005, is acknowledged. The drawing depicting Figure 3 is acceptable; however, the drawing depicting Figure 2 is not because in both instances "SEQ ID NO." is misspelled as "SEQ IS NO.".

Allowable Subject Matter

8. With regard to the preceding Office action mailed December 7, 2004, the indicated allowability of claims 4 and 5 is withdrawn in view of the new grounds of rejection of those claims, which is set forth herein.

Response to Amendment

9. At page 4 of the amendment filed November 10, 2005, Applicant has stated, "the Examiner agreed that a polynucleotide whose sequence is SEQ ID NO:2 is patentable". Notably SEQ ID NO: 2 is an amino acid sequence, and contrary to any implication that a claim drawn to polypeptide comprising SEQ ID NO: 2 is patentable, it is not. During the interview the Examiner explained the reasons why such a claim is not patentable over the prior art of record, but noted that since the polynucleotide sequence of SEQ ID NO: 3 is free of the prior art, the claims could be amended to overcome the rejections that are currently of record over the prior art. As explained in the Interview Summary mailed November 9, 2005, the Examiner proposed entry of an examiner's amendment, which would place this application in condition for allowance, but Applicant's representatives opted not to authorize its entry in favor of filing a supplemental amendment.

Grounds of Objection and Rejection Withdrawn

10. Without acquiescing to Applicant's arguments, the rejections of claims under 35 U.S.C. §§ 102 or 103, as being anticipated by Grey et al., as evidenced by Schor et al., or obvious Grey et al., as evidenced by Schor et al., in view of Bendig, for the reasons set forth in sections 25 and 29 of the preceding Office action have been withdrawn in favor of the new grounds of rejection set forth below.

Otherwise, unless specifically reiterated below, Applicant's amendment and/or arguments filed June 8, 2005, August 18, 2005, and/or November 10, 2005, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed December 7, 2004.

Grounds of Objection and Rejection Maintained

Drawings

11. The objection to the drawing sheet setting forth Figure 2 (Part 2), because "SEQ ID NO." is misspelled as "SEQ IS NO." in both instances, is maintained. As noted above, although a replacement sheet was filed June 8, 2005, this issue has not been resolved. Appropriate correction is required.

Specification

12. The objection to the specification, because the use of improperly demarcated trademarks, is maintained. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Although it appears Applicant has made a *bona fide* attempt to correct this issue, another example of an improperly demarcated trademark is found at page 47, line 19, of the substitute specification filed June 8, 2005, namely pBlueScript™.

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at <http://www.uspto.gov/web/menu/search.html>.

Claim Rejections - 35 USC § 112

Art Unit: 1643

13. The rejection of claims 9 and 61 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained.

Claims 9 and 61 are indefinite because the claims recite a limitation that the polypeptide has "the migration stimulating factor activity of the polypeptide having the amino acid sequence of SEQ ID NO: 2". Although claims 9 and 61 depend directly or directly from claim 1, which defines the migration stimulation activity of a polypeptide having the amino acid sequence of SEQ ID NO: 2 as "[the] ability to stimulate adult skin fibroblast migration into collagen gel", claims 9 and 61 are not necessarily so limited, since claims 9 and 61 are only required to be processes comprising culturing a host cell comprising a polynucleotide according to claim 1. In other words, although the host cells cultured in the claimed processes comprise a polynucleotide according to claim 1, the recitation does not limit the method to a process for making a polypeptide having "[the] ability to stimulate adult skin fibroblast migration into collagen gel", because the polypeptide made according to the claimed process is not necessarily a polypeptide encoded by a polynucleotide according to claim 1. Furthermore, as explained in the preceding Office action, the specification does not clearly and particularly define what functional activity or activities constitute "the migration stimulating factor activity" of the polypeptide of SEQ ID NO: 2. Accordingly, the metes and bounds of the subject matter that Applicant regards as the invention cannot be ascertained with the requisite degree of particularity and clarity, so as to permit the skilled artisan to determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

14. The rejection of claims 1, 7, 8, 9, 60, and 61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

At pages 11 and 12 of the amendment filed June 8, 2005, and at pages 11 and 12 of the amendment filed August 18, 2005, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

The claims are directed to nucleic acid molecules encoding a genus of structurally and functionally variable polypeptides. More specifically the claims are directed to nucleic acid molecules having a sequence with at least 90% homology to a polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 and encoding a polypeptide that has at least 30% of the "migration stimulation factor activity" of a polypeptide comprising SEQ ID NO: 2 and which elicits antibodies that recognize "migration stimulation factor" but not fibronectin. Moreover, the claims are not limited to nucleic acid molecules comprising the disclosed polynucleotide sequences that encode a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, but rather encompass nucleic acid molecules encoding variants of this polypeptide.

Although the members of the claimed genus of nucleic acid molecules necessarily comprise a polynucleotide sequence that is at least 90% homologous to a polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, the members are not required to have any particular degree of identity to the disclosed polynucleotide sequence of SEQ ID NO: 3, which encodes the amino acid sequence of SEQ ID NO: 2. Accordingly, the claims are directed to a genus of nucleic acid molecules that vary substantially in structure.

Although the members of the claimed genus of nucleic acid molecules necessarily encode polypeptides having at least 30% of the "migration stimulation factor activity" of a polypeptide comprising SEQ ID NO: 2, which elicits antibodies that recognize "migration stimulation factor", but not fibronectin, the polypeptides themselves are not required to have any degree of structural homology (i.e., similarity) or identity to the amino acid sequence of SEQ ID NO: 2. Accordingly, the claims are directed to a genus of nucleic acid molecules that vary substantially in structure and encode

polypeptides, which although commonly having at least 30% of the "migration stimulation factor activity" of a polypeptide comprising SEQ ID NO: 2 and commonly having the ability to elicit antibodies that recognize "migration stimulation factor", but not fibronectin, vary substantially in structure.

Although the members of the claimed genus of nucleic acid molecules necessarily encode polypeptides having at least 30% of the "migration stimulation factor activity" of a polypeptide comprising SEQ ID NO: 2, the members of the genus cannot be immediately envisioned, recognized or distinguished from other nucleic acid molecules encoding other proteins. The specification describes only one polypeptide encoded by the claimed genus of nucleic acid molecules, namely the polypeptide of SEQ ID NO: 2. Neither the nucleic acid molecules encoding the polypeptide of SEQ ID NO: 2 (e.g., the nucleic acid molecule of SEQ ID NO: 3) nor the polypeptide itself are described in sufficient and detailed manner, so as to reasonably be considered representative of the genus, as a whole, since there is no disclosure of a particularly identifying (i.e., substantial) structural feature shared by at least most of the polypeptides encoded by the claimed nucleic acid molecules that correlates with the polypeptides' ability to stimulate adult skin fibroblasts migration into collagen gel, which is at least 30% of the same activity of a polypeptide comprising SEQ ID NO: 2.

Although the members of the claimed genus of nucleic acid molecules necessarily encode polypeptides that elicit antibodies that recognize "migration stimulation factor", but not fibronectin, the members of the genus cannot be immediately envisioned, recognized or distinguished from other nucleic acid molecules encoding other proteins. Again, the specification describes only one polypeptide encoded by the claimed genus of nucleic acid molecules, namely the polypeptide of SEQ ID NO: 2. Neither the nucleic acid molecules encoding the polypeptide of SEQ ID NO: 2 (e.g., the nucleic acid molecule of SEQ ID NO: 3) nor the polypeptide itself are not described in sufficient and detailed manner, so as to reasonably be considered representative of the genus, as a whole, since there is no disclosure of the presence of a shared, particularly identifying structural feature, which in this case is necessarily a common antigenic determinant (i.e., the epitope to which an antibody that recognizes the protein encoded

Art Unit: 1643

by the claimed nucleic acid molecule, which is not presented by fibronectin), that correlates with their shared “migration stimulation factor activity”. Moreover, the recitation of a limitation requiring the polypeptide encoded by the members of the claimed genus of nucleic acid molecules to elicit an antibody that binds specifically to “migration stimulation factor”, but not fibronectin, would not reasonably convey to the skilled artisan that, as of the filing date sought, the Applicant had possession of the claimed invention, because the recitation does not provide a description of any uniquely defining or identifying feature that is common to at least a substantial number of members of the claimed genus, which would descriptively set the genus apart from just any polypeptide encoded by a nucleic acid molecule having the required similarity (i.e., at least 90% homology) to the reference amino acid sequence encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2.

With particular regard to claims 9 and 61, the claims are directed to methods for making a polypeptide having at least 30% of the “migration stimulation factor activity” of a polypeptide comprising SEQ ID NO: 2, said methods comprising culturing a cell comprising a polynucleotide according to claim 1, but the polypeptide produced by the claimed methods is not necessarily a polypeptide encoded by the polynucleotide according to claim 1. Thus, claims 9 and 61 are directed to methods for making structurally variant polypeptides encoded by any nucleic acid molecule of which said host cell is comprised, which commonly have at least 30% of the “migration stimulation factor activity” of a polypeptide comprising SEQ ID NO: 2.

The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See Noelle v. Lederman, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Insofar as the claims are directed to structurally varying nucleic acid molecules encoding polypeptides that differ both structurally and functionally from the disclosed polypeptides comprising the amino acid sequence of SEQ ID NO: 2, the specification fails to describe the claimed invention with the requisite detail and particularity that is

necessary to satisfy the written description requirement set forth under 35 U.S.C. 112, first paragraph. “[G]eneralized language may not suffice if it does not convey the detailed identity of an invention.” *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes the genus of nucleic acid molecules. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

Even whilst the nucleic acid molecules encompassed by the claims encode polypeptides that have recognizable functions, it is again aptly noted that the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability stimulate adult skin fibroblasts migration into collagen gel, which is at least 30% of the same activity of a polypeptide comprising SEQ ID NO: 2, and to elicit an antibody that cross-reacts with the polypeptide of SEQ ID NO: 2 without binding fibronectin, does not provide an adequate written description of the genus. See *The Regents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

In addition, although the skilled artisan could potentially screen candidate nucleic acid molecules to identify those that encode polypeptides that are encompassed by the claims, which have those recognizable functions, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Finally, Applicant is again reminded that Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "Written Description" Requirement (66 FR 1099-1111, January 5, 2001) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Because the claims encompass a genus of nucleic acid molecules encoding polypeptides, which vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

Thus, while the disclosure might be considered to provide *ipsis verbis* support for the claimed invention, the Federal Circuit has explained that *in ipsis verbis* support does not *per se* establish compliance with the written description requirement:

Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). See also: *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 1892 (CA FC 2004).

15. The rejection of claims 1, 7, 8, 9, 60, and 61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** an isolated, recombinant nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, an isolated, recombinant nucleic acid molecule comprising the polynucleotide sequence of SEQ ID NO: 3 from the nucleotide at position 57 through the nucleotide at position 1982, a isolated replicable vector comprising any of said polynucleotide sequences, an isolated host cell comprising said vector, and a method for producing said polypeptide by a process comprising culturing said host cell and isolating said polypeptide, or any nucleic acid molecule taught by the prior art, **does not reasonably provide enablement for making and using** a nucleic acid molecule having a polynucleotide sequence that is at least 90% homologous to a recombinant polynucleotide sequence encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, which stimulates adult skin fibroblasts migration into collagen gel with at least 30% of the same activity of a polypeptide comprising SEQ ID NO: 2 and elicits an antibody that cross-reacts with the polypeptide of SEQ ID NO: 2 without binding fibronectin, a replicable vector comprising said polynucleotide sequence, an isolated host cell comprising said polynucleotide sequence, or a method for producing a polypeptide that stimulates adult skin fibroblasts migration into collagen gel with at least 30% of that activity of a polypeptide comprising SEQ ID NO: 2, said method comprising culturing a host cell comprising said polynucleotide sequence and isolating the polypeptide. The

Art Unit: 1643

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/or the invention commensurate in scope with these claims.

At pages 11 and 12 of the amendment filed June 8, 2005, and at pages 11 and 12 of the amendment filed August 18, 2005, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

MPEP § 2164.01 states:

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

As explained above in the rejection of claims under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, the claims are directed to nucleic acid molecules of considerable structural variability, which encode

Art Unit: 1643

polypeptides that differ markedly, both in structure and function. As explained in the preceding Office action, the state of the art, the level of skill in the art, and the unpredictability in the art are such that absent guidance, direction, and exemplification that is more reasonably commensurate in scope with the scope of the claims, the skilled artisan, at the time the application was filed, could not without undue and/or unreasonable experimentation make and/or use the claimed invention. This position is supported by references cited in the preceding Office action, including Skolnick et al. (of record), Burgess et al. (of record), and Lazar et al. (of record).

The claims are directed to nucleic acid molecules that encode variants of the disclosed polypeptide of SEQ ID NO: 2, which have or retain at least 30% of the ability of the polypeptide of SEQ ID NO: 2 to stimulate adult skin fibroblasts to migrate into collagen gel, as measured using an assay described by Picardo et al. (of record). However, as explained previously, the specification fails to teach which amino acid residues of SEQ ID NO: 2 are critical to this particular function of the polypeptide of SEQ ID NO: 2. Moreover, the specification fails to teach by which other amino acids such critical residues can be replaced without loss of activity. Absent such necessary guidance and direction, because the skilled artisan cannot reliably and accurately predict the effects of amino acid substitutions, deletions, or insertions in the amino acid sequence of a given polypeptide, the disclosure would not be sufficient to have enabled the skilled artisan at the time the application was filed to make, and therefore use, the claimed invention.

Furthermore, there is no factual evidence of record that reasonably supports any assertion that the mere presence of a common antigenic determinant correlates with, or determines a common "migration stimulation factor activity" of any polypeptide encoded by nucleic acid molecules having sequences that are at least 90% homologous (i.e., similar to) a nucleic acid molecule encoding a polypeptide comprising SEQ ID NO: 2. Therefore, although the members of the claimed genus of nucleic acid molecules necessarily encode polypeptides that elicit antibodies that recognize "migration stimulation factor", but not fibronectin, it is submitted that the members of the genus cannot be distinguished from other nucleic acid molecules encoding other proteins

simply by using the encoded polypeptide to elicit antibodies and then determining if the antibodies bind the polypeptide without binding fibronectin. As such, the requirement that the claimed nucleic acid molecules encode antigenically related polypeptides does not remedy the insufficiency of the guidance and direction that would otherwise, if present and sufficient, enable the skilled artisan to make the claimed nucleic acid molecules encoding variants of the polypeptide of SEQ ID NO: 2.

Echoing this fact, Takada et al. (*Mol. Endocrinol.* 2000; **14** (5): 733-740) teaches that the lack of predictability in the art remains, despite technological advances and a better understanding of the structure-function relationship; see entire document (e.g., the abstract). Takada et al. teaches their work illustrates that a single amino acid change may be sufficient to cause the acquisition of a new ligand binding specificity as well as to suppress recognition of a previous ligand, extending observations by others who showed that changes in one or several amino acids can result in marked alterations in activity and function of nuclear receptors (page 738, column 1). Notably, Takada et al. teaches that the functional consequence of amino acid substitution may be rather subtle, since the variants of the receptors were still able to bind to the promoter of the reporter construct and activate transcription in the presence of some ligands but not others; see, e.g., page 739, Figure 5. Takada et al. teaches the difference in ligand binding specificity caused by the amino acid changes results in the variants having the activity of different member of the family of proteins; see, e.g., the abstract. Thus, Takada et al. discloses that seemingly subtle differences resulting from amino acid differences, such as changes in ligand binding specificity, may cause variants of a protein to have a function that differs markedly from that of the protein. Accordingly, depending upon the assay used to assess the activity of the proteins and its variants, the effects of amino acid sequence variation may not be immediately recognized or appreciated, since the variants may appear to function normally otherwise, but in actuality have substantially different functions.

Even more recently, Guo et al. (*Proc. Natl. Acad. Sci. USA.* 2004 Jun 22; **101** (25): 9205-9210) have calculated the probability that a random amino acid substitution, such as that which might occur naturally during aging or as a consequence of evolution

Art Unit: 1643

or disease, will cause inactivation of a protein; see entire document (e.g., the abstract). Guo et al. reports this probability was found to be $34\% \pm 6\%$ (abstract); that is, 34% of random mutations in the sequence of a protein are predicted to cause the inactivation of the protein. Guo et al. observed that various residues are differentially sensitive to substitutions, but the tolerance of the entire protein to random change can be defined by the probability that any given random amino acid substitution will inactivate the protein (i.e., the so-called "x factor") (page 9209, column 2). Not surprisingly, evolutionarily conserved residues showed low substitutability indices (abstract).

Thus, Lazar et al. (of record), for example, shows that even a single, conservative amino acid change can cause substantial changes in the activity of a protein, so it is evident that the skilled artisan cannot predict the functional consequences of amino acid substitutions and must determine those consequences empirically; and since Guo et al. (*supra*) shows that amino acid substitutions are remarkably likely to cause inactivation of the protein, it is even more apparent that the functional consequences of the amino acid differences must be ascertained before any given variant of a protein can be used in the same manner in which the protein having a known function is used.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), there is a preponderance of factual evidence of record that indicates the disclosure would not be sufficient to have enabled the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

16. The rejection of claims 1, 7-9, 60, and 61 under 35 U.S.C. 102(b), as being anticipated by WO 94/16085 A2 (of record), is maintained.

At page 14 of the amendment filed June 8, 2005, and at page 14 of the amendment filed August 18, 2005, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but are not found persuasive for the following reasons:

Claim 1 is drawn to a recombinant polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, or alternatively to a polynucleotide having a sequence with at least 90% homology to a polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 and encoding a polypeptide that has at least 30% of the "migration stimulation factor activity" of a polypeptide comprising SEQ ID NO: 2 and which elicits antibodies that recognize "migration stimulation factor" but not fibronectin. Claim 7 is drawn to a replicable vector comprising a recombinant polynucleotide according to claim 1. Claims 8 and 60 are drawn to an isolated host cell comprising a recombinant polynucleotide according to claim 1, or a replicable vector according to claim 7, respectively. Claims 9 and 61 are drawn to methods for making a polypeptide having at least 30% of the "migration stimulation factor activity" of a polypeptide comprising SEQ ID NO: 2, said methods comprising culturing a host cell comprising a polynucleotide according to claim 1, or a host cell according to claim 60, respectively.

"Homology" is defined, for example, by Merriam-Webster Online Dictionary, which available on the Internet at <http://www.merriam-webster.com/>, as "similarity of nucleotide or amino-acid sequence in nucleic acids, peptides, or proteins" (copyright 2005 by Merriam-Webster, Incorporated). Homology or similarity of nucleic acid sequences may be evaluated by relatively subjective criterion, or it may be objectively measured using any of wide variety of differing criterion.

Accordingly, the claims are not limited to nucleic acid molecules comprising a polynucleotide sequence that is at least 90% identical to any particular polynucleotide sequence encoding the amino acid sequence of SEQ ID NO: 2, such as the polynucleotide sequence of SEQ ID NO: 3. Rather the claims are directed to a genus of structurally varying nucleic acid molecules that are somehow determined to be 90% homologous (i.e., similar) to a polynucleotide sequence encoding the amino acid sequence of SEQ ID NO: 2

WO 94/16085 A2 (Irani) teaches an isolated, recombinant nucleic acid molecule comprising a polynucleotide that encodes a polypeptide that is 97.1% identical to amino acid sequence of SEQ ID NO: 2; see entire document (e.g., SEQ ID NO: 2). Irani teaches the polypeptide encoded by the disclosed nucleic acid molecule is produced by a process comprising culturing a host cell comprising a replicable vector comprising a polynucleotide sequence encoding the polypeptide and purifying the polypeptide; see, e.g., page 8, line 27, through page 15, line 12.

When compared to the polynucleotide sequence of SEQ ID NO: 3, which is the disclosed polynucleotide sequence encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, the polynucleotide sequence disclosed by the prior art (i.e., SEQ ID NO: 1) has a “best local similarity” of 97.1%; see the attached copy of part of the U.S.P.T.O. search report “us-09-581-651d-3.rni” (Result 3), which was generated by searching the Office’s “Issued Patents NA” database using SEQ ID NO: 3 as a query.

Although Irani et al. does not expressly teach the polypeptide encoded by the disclosed nucleic acid molecule has at least 30% of the “migration stimulation factor activity” of a polypeptide comprising SEQ ID NO: 2 and elicits antibodies that recognize “migration stimulation factor” but not fibronectin, the Office does not have the facilities for examining and comparing Applicant’s product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed polynucleotide, replicable vector, and host cell, or for examining and comparing Applicant’s process with process of the prior art to establish that the claimed method for making a polypeptide and the methods of the prior art produce distinguishable products.

Given the fact that the nucleic acid molecule disclosed by the prior art encodes a polypeptide having an amino acid sequence that is 94.8% identical to amino acid sequence of SEQ ID NO: 2, the claimed products and processes are deemed the same as those disclosed by the prior art, absent a showing of any difference.

In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products and processes are different than those taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte*

Gray, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

New Grounds of Rejection

Claim Rejections - 35 USC § 101

17. Claims 1, 4, 5, and 7 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1, 4, and 5 are specifically drawn to “recombinant” polynucleotides, whereas claims 7 is drawn to a replicable vector comprising a polynucleotide as defined in claim 1.

The Merriam-Webster's Online Dictionary, 10th Edition (copyright © 2005 by Merriam-Webster, Inc.), which is available on the Internet at <http://www.m-w.com/>, defines the term “recombinant” as “relating to or containing recombinant DNA”.

Because claims 1, 4, 5, and 7 are drawn to recombinant polynucleotides and replicable vectors comprising such polynucleotides, *which are not necessarily isolated*, the claims are broadly but reasonably interpreted to encompass nucleic acid molecules and replicable vectors that are present in cells, which are not isolated but rather comprised *within* an organism, including a human. Support for this interpretation of the claims is found throughout the specification; for example, at page 44, lines 10 and 11, the specification, as originally filed, contemplates the use of gene therapy to administer to patients (i.e., humans) the claimed replicable vector comprising the claimed nucleic acid sequence encoding the disclosed polynucleotide. Host cells comprised within the patient are “transformed” or “transfected” with the recombinant nucleic acid molecules encoding the polypeptide, or replicable vectors (e.g., retroviral vectors) comprising the polynucleotide sequences of such nucleic acid molecules; see, e.g., page 12, line 23, through page 13, line 28. Accordingly, the claims encompass such recombinant nucleic acid molecules and replicable vectors, which are comprised within the cells of treated patients.

MPEP § 2105 [R-1] states:

Art Unit: 1643

~~If the broadest reasonable interpretation of the claimed invention as a whole encompasses a human being, then a rejection under 35 U.S.C. 101 must be made indicating that the claimed invention is directed to nonstatutory subject matter.~~

With further regard to claims 1, 4, and 5, it is aptly noted the Merriam-Webster's Online Dictionary, 10th Edition (copyright © 2005 by Merriam-Webster, Inc.) provides an alternative definition of the "recombinant", namely "relating to or exhibiting genetic recombination". Given this definition, it is not apparent that the claimed subject matter is distinguishable from a naturally occurring polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, such as the messenger RNA (mRNA) molecule of which human cells are naturally comprised, which encodes the polypeptide of SEQ ID NO: 2. Accordingly, giving the claims the broadest, reasonable interpretation that is consistent with both the specification and that which the skilled artisan would have, the claims are drawn to non-statutory subject matter (i.e., a naturally occurring product).

Moreover, claim 1 is drawn to a recombinant polynucleotide encoding a polypeptide, or alternatively to a polynucleotide, albeit not necessarily recombinant or isolated having a sequence with at least 90% homology to a polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 (e.g., a sequence at least 90% homologous to SEQ ID NO: 3) and encoding a polypeptide that has at least 30% of the "migration stimulation factor activity" of a polypeptide comprising SEQ ID NO: 2 and which elicits antibodies that recognize "migration stimulation factor" but not fibronectin.

These issues can be remedied by amending claims 1, 4, 5, and 7 to recite the limitation "isolated" before "recombinant polynucleotide" or "replicable vector".

Claim Rejections - 35 USC § 112

18. Claims 1, 7-9, 60, and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Art Unit: 1643

Claim 1 is drawn a polynucleotide having a sequence with at least 90% homology to a polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 and encoding a polypeptide that has at least 30% of the migration stimulation factor activity of a polypeptide comprising SEQ ID NO: 2 and which elicits antibodies that recognize "migration stimulation factor" but not fibronectin. Claims 7-9, 60, and 61 depend from claim 1.

The claims are indefinite because claim 1 uses the term "migration stimulation factor" to define the polypeptide by which antibodies elicited by the claimed polypeptide are recognized without also recognizing fibronectin. The use of laboratory designations only to identify a particular polypeptide renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct polypeptides. In the absence of clear and particular identification of the polypeptide to which the claims are directed, the metes and bounds of the subject matter that Applicant regards as the invention are sufficiently delineated, so as to permit the skilled artisan to determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

This issue may be remedied by amending claim 1 to reference to the amino acid sequence of "migration stimulation factor" to which the claims are directed because the amino acid sequence of a polypeptide is a unique identifier that unambiguously defines a given polypeptide.

19. Claims 1, 4, 5, and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** an *isolated*, recombinant nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, an *isolated*, recombinant nucleic acid molecule comprising the polynucleotide sequence of SEQ ID NO: 3, and an *isolated* replicable vector comprising the polynucleotide sequence of any of the aforementioned nucleic acid molecules, **does not reasonably provide enablement for making and using** any such *non-isolated* nucleic acid molecules or replicable vectors encompassed by the claims. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

As explained in the above rejection of claims 1, 4, 5, and 7 under 35 U.S.C. 101, the claims encompass the polynucleotides according to claim 1 or the replicable vectors (e.g., a recombinant retrovirus) according to claim 7, which have been introduced into cells comprised within an organism, including humans that are treated with such polynucleotides and replicable vectors. Again, support for this interpretation of the claims is found throughout the specification, as originally filed (e.g., page 12, line 23, through page 13, line 28; page 42, lines 6-8; and page 44, lines 10 and 11).

However, as explained in section 21 of the preceding Office action with regard to claim 8, the amount of guidance, direction, and exemplification set forth in the specification would not be sufficient to enable the skilled artisan to make and use the claimed invention without undue and/or unreasonable experimentation. This position was supported by the teachings of Houdebine (of record), Verma et al. (of record) Amalfitano et al. (of record), Pandha et al. (of record), and the memorandum dated January 14, 2003, by Dr. Patterson of the U.S. Department of Health and Human Services. This ground of rejection set forth in the preceding Office action is herein reiterated with respect to claims 1, 4, 5, and 7, as these claims are broadly but reasonably interpreted to encompass polynucleotides and replicable vectors comprising polynucleotide sequences encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, which have been introduced into cells of which animals, including humans are comprised.

Notably it would be remedial to amend claims 1, 4, 5, and 7 to recite the limitation "isolated" before "recombinant polynucleotide" or "replicable vector".

20. Claims 1, 7-9, 60, and 61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a “new matter” rejection.

Claim 1 recites, “wherein migration stimulation factor activity refers to ability to stimulate adult skin fibroblast migration into collagen gel”.

At page 5 of the amendment filed November 11, 2005, Applicant has asserted that written support for the language of the claim 1 is found throughout the specification but, in particular, at page 9.

Although the specification, as originally filed, describes assessing the activity of members of a genus of “MSF polypeptides” in “bioassays based on its stimulation of adult skin fibroblast migration, for example, as in Picardo *et al* (1991) *The Lancet* 337, 130-133” (page 10, lines 1-6), this disclosure is insufficient to provide proper written support for defining the migration stimulation factor activity of the genus of polypeptides to which the claims are directed as “[the] ability to stimulate adult skin fibroblast migration **into collagen gel**” (emphasis added).

Furthermore, although the specification cites Picardo *et al.* as describing such a bioassay, MPEP § 608.01(p) does not provide for the incorporation by reference of essential material by reference to non-patent publications. “Essential material” is defined as “that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112)”. The bioassay described by Picardo *et al.* is essential information because claim 1 presently recites, “wherein migration stimulation factor activity refers to ability to stimulate adult skin fibroblast migration into collagen gel”, and thus the disclosure of Picardo *et al.* describing such a bioassay is necessary to describe, if not enable, the claimed invention.

It is suggested this issue may be remedied by incorporating relevant portions of the disclosure of Picardo *et al.* (of record), which provide sufficient written support for the present claim language. Applicant should do so by amending the specification to include this material incorporated by reference to Picardo *et al.*, and the amendment must be accompanied by an affidavit or declaration executed by Applicant, or a practitioner representing Applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See In re

Art Unit: 1643

Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Claim Rejections - 35 USC § 102

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

22. Claims 1, 7-9, 60, and 61 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,830,700 A, as evidenced by the attached copy of part of the U.S.P.T.O. search report "us-09-581-651d-3.rni" (i.e., Result 2), which was generated by searching the Office's "Issued Patents NA" database using SEQ ID NO: 3 as a query.

Claim 1 is drawn to a recombinant polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, or alternatively to a polynucleotide having a sequence with at least 90% homology to a polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 and encoding a polypeptide that has at least 30% of the "migration stimulation factor activity" of a polypeptide comprising SEQ ID NO: 2 and which elicits antibodies that recognize "migration stimulation factor" but not fibronectin. Claim 7 is drawn to a replicable vector comprising a recombinant polynucleotide according to claim 1. Claims 8 and 60 are drawn to an isolated host cell comprising a recombinant polynucleotide according to claim 1, or a replicable vector according to claim 7, respectively. Claims 9 and 61 are drawn to methods for making a polypeptide having at least 30% of the "migration stimulation factor activity" of a polypeptide comprising SEQ ID NO: 2, said methods

comprising culturing a host cell comprising a polynucleotide according to claim 1, or a host cell according to claim 60, respectively.

"Homology" is defined, for example, by Merriam-Webster Online Dictionary, which available on the Internet at <http://www.merriam-webster.com/>, as "similarity of nucleotide or amino-acid sequence in nucleic acids, peptides, or proteins" (copyright 2005 by Merriam-Webster, Incorporated). Homology or similarity of nucleic acid sequences may be evaluated by relatively subjective criterion, or it may be objectively measured using any of wide variety of differing criterion.

Accordingly, the claims are not limited to nucleic acid molecules comprising a polynucleotide sequence that is at least 90% identical to any particular polynucleotide sequence encoding the amino acid sequence of SEQ ID NO: 2, such as the polynucleotide sequence of SEQ ID NO: 3. Rather the claims are directed to a genus of structurally varying nucleic acid molecules that are somehow determined to be 90% homologous (i.e., similar) to a polynucleotide sequence encoding the amino acid sequence of SEQ ID NO: 2

U.S. Patent No. 5,830,700 A (Irani) teaches an isolated, recombinant nucleic acid molecule comprising a polynucleotide that encodes a polypeptide that is 97.1% identical to amino acid sequence of SEQ ID NO: 2; see entire document (e.g., SEQ ID NO: 1). Irani teaches the polypeptide encoded by the disclosed nucleic acid molecule is produced by a process comprising culturing a host cell comprising a replicable vector comprising a polynucleotide sequence encoding the polypeptide and purifying the polypeptide; see, e.g., column 5, line 54, through column 8, line 44.

When compared to the polynucleotide sequence of SEQ ID NO: 3, which is the disclosed polynucleotide sequence encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, the polynucleotide sequence disclosed by the prior art has a "best local similarity" of 97.1%; see the attached copy of part of the U.S.P.T.O. search report "us-09-581-651d-3.mi" (Result 2), which was generated by searching the Office's "Issued Patents NA" database using SEQ ID NO: 3 as a query.

Although Irani et al. does not expressly teach the polypeptide encoded by the disclosed nucleic acid molecule has at least 30% of the "migration stimulation factor

activity” of a polypeptide comprising SEQ ID NO: 2 and elicits antibodies that recognize “migration stimulation factor” but not fibronectin, the Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed polynucleotide, replicable vector, and host cell, or for examining and comparing Applicant's process with process of the prior art to establish that the claimed method for making a polypeptide and the methods of the prior art produce distinguishable products.

Given the fact that the nucleic acid molecule disclosed by the prior art encodes a polypeptide having an amino acid sequence that is 94.8% identical to amino acid sequence of SEQ ID NO: 2, the claimed products and processes are deemed the same as those disclosed by the prior art, absent a showing of any difference.

In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products and processes are different than those taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

23. Claim 9 is rejected under 35 U.S.C. 102(b), as being anticipated by Grey et al. (of record), as evidenced by Schor et al. (*Breast Cancer Res.* 2001; **3**: 373-379), GenBank™ Accession No. AJ276395, and UniProtKB/Swiss-Prot™ Accession No. P02751.

Claim 9 is drawn to a method for making a polypeptide having at least 30% of the migration stimulation activity of the polypeptide having the amino acid sequence of SEQ ID NO: 2, said method comprising culturing a host cell comprising a polynucleotide according to claim 1.

As explained in the below rejection of claim 1 under 35 U.S.C. § 101, claim 1 encompasses a naturally occurring nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, such as the gene or messenger RNA (mRNA) transcribed from the gene encoding the polypeptide, which is expressed

Art Unit: 1643

naturally in certain cells. As evidenced by Schor et al., GenBank™ Accession No. AJ276395, and UniProtKB/Swiss-Prot™ Accession No. P02751, Grey et al. teaches culturing cells comprising such naturally occurring nucleic acid molecules encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2; see, e.g., page 2438, column 2, through page 2439, column 1. Grey et al. teaches isolating the polypeptide expressed by the cultured cells; see, e.g., page 2439, columns 1 and 2. Because the polypeptide comprises the amino acid sequence of SEQ ID NO: 2, it is expected to have at least 30% of the migration stimulation activity of the polypeptide having the amino acid sequence of SEQ ID NO: 2.

For further clarity, a polynucleotide according to claim 1 is not isolated, nor is it necessarily recombinant. Claim 1 is alternatively drawn a polynucleotide, albeit not necessarily recombinant, having a sequence with at least 90% homology to a polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 and encoding a polypeptide that has at least 30% of the migration stimulation factor activity of a polypeptide comprising SEQ ID NO: 2 and which elicits antibodies that recognize "migration stimulation factor" but not fibronectin. Nevertheless, even if claim 1 is limited to a "recombinant" polynucleotide, as explained in greater depth and detail below in the rejection of claim 1 under 35 U.S.C. § 101, a "recombinant" polynucleotide cannot be distinguished from a naturally occurring nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, such as the gene or mRNA transcribed from the gene encoding the polypeptide, which are found in the cells such as those disclosed by Grey et al.

In traversing the ground of rejection of claims under 35 U.S.C. § 102, as being anticipated by Grey et al., as evidenced by Schor et al. (*Cancer Res.* 2003 Dec; **63** (24): 8827-8836) (of record), which was set forth in the preceding Office action, Applicant argued that there is no evidence that Grey et al. necessarily discloses a protein having the amino acid sequence of SEQ ID NO: 2; see, e.g., page 13 of the amendment filed June 8, 2005. Moreover, Applicant contended the polypeptide disclosed by Grey et al. may not be the disclosed polypeptide having the amino acid sequence of SEQ ID NO: 2, since it could be another polypeptide, such as the

Art Unit: 1643

polypeptide disclosed by database EMBL Accession No. AJ535086, which comprises 15 amino acids not present in the amino acid sequence of SEQ ID NO: 2, as depicted in Figure 2. Applicant stated the amino acid sequence encoded by the polynucleotide sequence of EMBL Accession No. AJ535086 is 657 amino acids in length, whereas the amino acid sequence depicted in Figure 2 (i.e., SEQ ID NO: 2) is only 642 amino acids.

Without acquiescing to Applicant's arguments, it is herein noted that Schor et al. (*Breast Cancer Res.* 2001; **3**: 373-379) teaches the polynucleotide sequence of a complementary DNA molecule encoding "MSF", the 70 kDa polypeptide first purified by Grey et al., was submitted to the database EMBL under the accession number AJ276395; see entire document (e.g., page 376, columns 1 and 2). According to EMBL/GenBank™ Accession No. AJ276395, the amino acid sequence that is encoded by the disclosed polynucleotide sequence is reported in database UniProtKB/Swiss-Prot™ under the accession number P02751. According to UniProtKB/Swiss-Prot™ Accession No. P02751, the amino acid sequence of the alternative splice form-2, designated "MSF FN-70" and described by Schor et al. (*Breast Cancer Res.* 2001; **3**: 373-379)) is 642 amino acids.

The Examiner cannot account for the disparity between the amino acid sequence reported by Schor et al. as EMBL/GenBank™ Accession No. AJ276395 (i.e., the 642 amino acid sequence) and amino acid sequence, also reported by Schor et al., of EMBL Accession No. AJ535086 (i.e., the 657 amino acid sequence). Nevertheless, as evidenced by Schor et al. (*Breast Cancer Res.* 2001; **3**: 373-379) and corresponding disclosures in the databases, it appears that the 70 kDa polypeptide produced by the fibroblasts cultured by Grey et al. is the polypeptide of SEQ ID NO: 2.

Again, in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products and processes are different than those taught by the prior art. *See In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Claim Rejections - 35 USC § 103

Art Unit: 1643

24. Claims 1, 7-9, 60, and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grey et al. (of record), as evidenced by Schor et al. (*Breast Cancer Res.* 2001; 3: 373-379), GenBank™ Accession No. AJ276395, and UniProtKB/Swiss-Prot™ Accession No. P02751, in view of Bendig (of record).

Grey et al. and Bendig teach that which is set forth in section 29 of the preceding Office action.

As explained in the above rejection of claim 9 under 35 U.S.C. 102(b), as evidenced by Schor et al. (*Breast Cancer Res.* 2001; 3: 373-379), GenBank™ Accession No. AJ276395, and UniProtKB/Swiss-Prot™ Accession No. P02751, the 70 kDa polypeptide designated "migration stimulation factor (MSF)", which was isolated from cultured fibroblasts by Grey et al., is the polypeptide of SEQ ID NO: 2.

Grey et al. teaches, "[o]ur current efforts are directed toward cloning the gene for MSF and obtaining its complete sequence" (page 2441, column 1).

As explained in the preceding Office action, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have cloned a nucleic acid molecule encoding the polypeptide disclosed by Grey et al. because Grey et al. teaches efforts are underway to do exactly that, and Bendig teaches the methodology necessary to do so was well within the skill of the artisan of ordinary skill at the time the invention was made. Accordingly, as also explained in the preceding Office action, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to produce a host cell comprising a vector comprising the cloned polynucleotide sequence encoding the polypeptide by recombinant DNA technology in accordance with the teachings reviewed by Bendig and then culture the host cells and isolate the polypeptide produced by the host cells in the culture. Therefore, among other reasons, one ordinarily skilled in the art at the time of the invention would have been motivated to do so to facilitate production of the polypeptide by recombinant means.

Conclusion


25. Claim 29 is allowed; no other claim is allowed.

Art Unit: 1643

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
January 20, 2006